

OTHER GENETIC DISORDERS

Hemoglobinopathies

A hemoglobinopathy is a condition that affects the red blood cells and results from genetically determined changes in the molecular structure of hemoglobin. The hemoglobin electrophoresis test will reveal multiple hemoglobinopathy disorders with varying degrees of severity. Their effects range from mild anemia in Hemoglobin C disease, to severe pain episodes, growth delays, increased susceptibility to infections and persistent anemia in Sickle Cell Anemia (Hemoglobin SS). Hemoglobinopathies are inherited in an autosomal recessive pattern. Carriers of a single abnormal gene for these disorders are considered to have a trait. Persons with a trait will have red blood cells that contain a mixture of normal and abnormal hemoglobins. A hemoglobinopathy trait typically causes no disease or anemia under normal physiologic conditions.

Inheritance: Autosomal recessive

Estimated Incidence: 1:400 African Americans (sickling disorders)
1:2500 All Races/Ethnicities (sickling disorders)

Abnormal Screen Result: See chart below

The following table outlines retesting procedures for the most common results of the isoelectric focusing. It is important to remember that **PREMATURITY AND TRANSFUSIONS AFFECT TEST RESULTS**. Each type of hemoglobin in the infant's blood is identified by a particular letter on the test result (e.g. F=Fetal, A=Adult or normal, S=Sickle, V=unknown variant). The position of the letter represents the amount of the hemoglobin type present with the hemoglobin of greatest concentration listed first. (Example: "FSA" usually indicates a sickling disorder and "FAS" indicates trait). When rare hemoglobins are detected, specific instructions will be sent from CH.

Result	Indicative of	Sent to CHORI?
FS	sickle cell disease or Hb S β -0-thalassemia	Yes
FSC	Hb SC disease	Yes
FSA	Hb S β -+-thalassemia	Yes
FC	homozygous Hb C or Hb C β -0-thalassemia	Yes
FCA	Hb C β -+-thalassemia	Yes
FE	homozygous Hb E or Hb E β -0-thalassemia	Yes
FV	unknown hemoglobin variant	No
FF	prematurity, homozygous β thalassemia	Yes
FA + 10% or higher Barts	Hb H disease, α thalassemia	No
FAS, FAC, FAE, FAD, FAG, FAO, FAV, FA + less than 10% Barts, FA + fast band	various Hb traits/carriers	No
FA	normal Hb	No

Please consult with a pediatric hematologist for further recommendations.

Method of Notification:	All abnormal results are mailed to provider of record
Next Steps if Abnormal:	<p>Hemoglobinopathy disorders—Refer to pediatric hematologist. Consider initiation of penicillin prophylaxis upon receipt of newborn screening report if the hemoglobin pattern is FS.</p> <p>Hemoglobinopathy trait—Refer family to a sickle cell foundation for counseling.</p>
Neonatal Presentation:	None
Treatment:	Sickling disorders—Penicillin/antibiotic prophylaxis beginning in infancy and continuing through early childhood. Prompt evaluation/management of acute illness to lessen development of sickling crisis, particularly if fever is present. Appropriate pain management strategies (such as use of extra fluids, oral analgesics, comfort measure), including rapid triage if home management strategies are not sufficient. Transfusion may be necessary in certain instances. Medications to increase the production of fetal hemoglobin and lower leukocyte counts such as hydroxyurea may be used in certain children.

Special Considerations

Transfusion—Transfusion of red blood cells prior to drawing the newborn screening specimen will affect the hemoglobinopathy result. Repeat screening for hemoglobinopathies should be done 120 days after the last transfusion. If the date of the last transfusion is unknown, put the date of hospital discharge on the collection form next to “Transfused”.

Specimen Analysis at Reference Laboratory—The initial newborn screening bloodspots for infants with hemoglobinopathy results indicative of disease are sent to the Children’s Hospital Oakland Research Institute (CHORI) for more specific hemoglobinopathy analysis and genetic testing. The result of the CHORI analysis is sent to the provider of record upon receipt by the Laboratory.

Special Follow-up Assistance—The MUSC Pediatric Sickle Cell Program is assisting primary care providers across the state in an effort to ensure that infants identified with a sickling disorder are seen by a pediatric hematologist within the first six weeks of age. They coordinate activities with pediatric hematologists at the other children’s hospitals so that families are directed to the pediatric hematologist closest to them.

Participation in Sports or Extreme Physical Activity—Some persons with sickle cell trait may exhibit a sickling crisis associated with extreme physical activity. Precautions must be taken to lessen the chance for exertional rhabdomyolysis.

Cystic Fibrosis (CF)

Cystic fibrosis (CF) is characterized by pulmonary obstruction often accompanied by exocrine pancreatic dysfunction. A defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene leads to obstruction of exocrine pancreatic ducts which causes an increase in the pancreatic enzyme immunoreactive trypsinogen (IRT) in blood. CF usually affects the lungs, pancreas, intestine, liver and sweat glands, causing failure to thrive, steatorrhea, intestinal obstruction, salt loss, and progressive obstructive lung disease.

Inheritance:	Autosomal recessive
Estimated Incidence:	1:3900 (varies by ethnic group)
Abnormal Screen Result:	Elevated IRT
Method of Notification:	All abnormal results are mailed to provider of record
Next Steps if Abnormal:	Repeat IRT on filter paper and see infant to ascertain health status as soon as possible. If IRT is still elevated on repeat testing, consult pediatric pulmonologist for further instructions. Diagnosis by sweat testing at a CF Foundation accredited care center and/or DNA testing is necessary for final diagnosis. Initiate treatment as recommended by specialist.
Neonatal Presentation:	Usually none. Meconium ileus or volvulus may occur in 5-10 % of affected infants. Prolonged jaundice without other cause is more common than very early lung disease.
Treatment:	Chest physiotherapy to aid in airway clearance. Antibiotics/other medications to treat lung infections as needed. Pancreatic enzymes if indicated; vitamins; NaCl supplements. Close monitoring of growth parameters and use of nutritional supplements if needed to enhance/maintain appropriate growth/development.

Special Considerations

Premature/Sick Infants—The stress of prematurity and/or illness can lead to falsely elevated IRT test results.

Meconium Ileus—All infants with meconium ileus should be thoroughly evaluated for CF regardless of the IRT result. A normal IRT result does not rule out CF in these infants.

Prenatal Screening—The American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG) recommend that CF carrier screening be offered to non-Jewish Caucasians and to Ashkenazi Jews. Persons of other ethnicities should be informed about CF carrier screening. However, negative carrier status in either/both parents

does not definitively rule out the possibility of CF in an infant. Infants may have rare mutations that are not included in a standard CF DNA screening panel.

False Negative Test Results—Some infants with CF may have false negative IRT results.

Physicians must remain alert to clinical signs of CF in older infants despite normal initial screening results.

Severe Combined Immunodeficiency (SCID)

Low levels of T cell receptor excision circles (TRECs) are associated with Severe Combined Immunodeficiency (SCID). Other conditions associated with low TRECs include reticular dysgenesis, coronin-1A deficiency and thymic aplasia/complete DiGeorge syndrome. T lymphocytes fail to develop and the affected infant may also have impaired B lymphocyte function.

Inheritance: Autosomal recessive and X-linked

Estimated Incidence: 1:40,000 to 1:60,000

Abnormal Screen Result: Elevated Cq

Method of Notification: All abnormal results are called to provider of record and the Immune Disorder Specialist

Next Steps if Abnormal: **Potential medical emergency when TRECs are low and RNase P is within normal limits. The screening report will indicate Cq (Quantification Cycle) value instead of actual number of TRECs.** Cq is the number of cycles needed for the fluorescence of the amplified DNA to exceed the laboratory's established fluorescence threshold. **The Cq value of TRECs is inversely related to the copy number of TRECs in a specimen.** Specimens that have a low TREC content (low copy number) have a higher Cq value, because the specimens have to go through more thermal cycles to achieve fluorescence above the baseline.

See infant as soon as possible to ascertain health status. Consult pediatric specialist (immunology or pediatric infectious disease) and initiate diagnostic evaluation and treatment as recommended. Common diagnostic studies include specialized flow cytometry and molecular testing to determine specific mutations. In addition, repeat TREC on filter paper and send to the DHEC laboratory. Low TRECs with low RNase P may indicate DNA amplification failure. Prompt repeat screening is necessary to rule out SCID in these infants.

Neonatal Presentation: Usually none. Median age for onset of symptoms is 8 weeks of age.

Emergency Treatment: Usually none.

Standard Treatment: Bone marrow transplantation by 3 months of age is associated with the best outcomes for SCID. Infants with other conditions may be treated with medications.

Special Considerations

Infectious Disease Precautions—Parents should be instructed to avoid exposure of the infant to anyone with viral/bacterial illnesses until SCID is definitively ruled out. No vaccines should be given until cleared to do so by the specialist. The specialist may advise breastfeeding mothers to suspend breastfeeding while their blood is checked for anti-CMV IgG antibodies and

CMV DNA. These mothers should be encouraged to pump and freeze their breast milk during this time. Prompt resumption of breastfeeding is encouraged if the mother is seronegative. **Only leukoreduced, CMV negative, irradiated blood should be used if a transfusion is necessary.**

Premature/Sick Infants—Premature infants may have low TRECs due to immaturity of the immune system. Prompt repeat screening is indicated. The pediatric specialist (immunology or pediatric infectious disease) may recommend flow cytometry if TRECs are low in a second blood spot specimen. Low TRECs may also be found in specimens obtained from infants who have undergone thymectomy/cardiac surgery if the specimen is collected after surgery.